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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,568	01/28/2004	Esther H. Chang	2474.0100001	8131

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EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
12/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,568	CHANG ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/18/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5-16 and 18-22 are pending and are under examination.

Objections to Specification withdrawn

The objections to the specification are withdrawn in view of Applicant's amendments to the Specification.

35 USC § 103(a) rejections withdrawn

The rejection of claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas in view of Jang et al and Darmon et al is withdrawn in view of the amendments to claim 1.

35 USC § 103(a) rejections withdrawn

The rejection of claims 5-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas in view of Jang et al and Darmon et al, and further in view of Xu et al is withdrawn in view of the amendments to claim 1.

35 USC § 103(a) rejections withdrawn

The rejection of claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas in view of Jang et al and Darmon et al is withdrawn in view of the amendments to claim 1.

NEW REJECTIONS: Based on the IDS and Amendments to claims 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

Claims 19 and 21 contains the trademark/trade names P6 and P30. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the P6and P30 accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 15, 16 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas (previously cited), in view of Jang et al (previously cited), Hayami et al (IDS, 1999) and Sumpter et al (General and Comparative Endocrinology, 1986, 62:367-376) as evidenced by Köhler et al (2002, IDS).

The claims are drawn to a method for evaluating the efficacy of a therapeutic agent in the body of a mammal comprising obtaining a first sample of whole blood. plasma or serum, wherein said first sample can contain a 17 kDa fragment of caspase 3, wherein said first sample has been obtained from said mammal before administration of said therapeutic agent to said mammal; purifying the first sample using column chromatography; assaying the first sample to determine the amount of the cleaved 17 kDa fragment present; administering said therapeutic agent to said mammal; obtaining a second sample of whole blood, plasma or serum,
from the mammal; purifying the second sample using column chromatograph; and assaying the second sample to determine the amount of said 17kDa fragment present; wherein the amount of cleaved 17 kDa subunit in the second sample is at least 1.5 to about 2 times the amount of said cleaved subunit in the first sample, wherein the mammal is tumor bearing, wherein the column chromatograph comprises a P6 or P30 column chromatograph.

Mascarenhas discloses that treatment of mice with mammary adenocarcinoma with insulin-like growth factor-binding protein 3 and doxorubicin increased caspase 3 activity and reduced tumor weight. (column 29 line 47-67, Table 5) compared to normal controls. Mascarenhas discloses that caspase 3 activity was indicative of apoptosis induced by treatment. (Id). Caspase 3 activity was increased by 1.5 – 2 fold over that of the control. (Id).

Mascarenhas does not disclose that treatment resulted in an increase in the cleaved 17 kDa fragment of caspase 3.

Jiang et al discloses that an increase in caspase 3 activity was the result of cleavage of the inactive proenzyme CPP-32 into the catalytically active 17 kDa protein

and a 12 kDa protein. (page 176, 1st and 2nd columns). Thus, both the 17k Da fragment of caspase 3, and caspase 3 activity are used as measures of apoptosis induced by therapeutic agents that stimulate apoptosis.

Hayami et al disclose that caspase 3 activity can be detected in serum (Table 1).

Sumpter et al disclose that a BioGel P6 column may be used to purify proteins from serum.

One of ordinary skill in the art would have been motivated to apply Jiang et al's disclosure that caspase 3 activity is the 17k Da fragment of caspase 3 to Mascarenhas treatment and detection of apoptosis by caspase 3 activity because both Mascarenhas and Jiang et al detect apoptosis by examining caspase 3 activity. It would have been *prima facie* obvious to combine Mascarenhas treatment and detection of apoptosis by caspase 3 activity with Jiang et al method of measuring apoptosis by caspase 3 activity to measure the effect of apoptosis inducing agents. Both an increase in caspase 3 activity and an increase in the amount of the 17k Da fragment of caspase 3 reflect an increase in apoptosis. Thus, caspase 3 activity and the amount of the 17k Da fragment of caspase 3 are just different indices of the same process. Indeed caspase 3 activity is just measuring the activity of the 17k Da fragment of caspase 3. As evidenced by Kohler, measuring caspase activity can be accomplished by either measuring the activated caspase by immunoblotting (measuring the 17k Da fragment of caspase) or by the cleavage of synthetic substrates (caspase 3 activity). (page 100 1st column to page 103 2nd column).

Applicants argue that there is no disclosure of detection of the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum as recited in the presently claimed inventions in any of the references cited by the Examiner. Applicants argue that Mascarenhas is limited to the use of enzymatic techniques to determine the presence, not the amount, of caspase. Applicants argue that detection of the amount of the 17 kDa fragment of caspase 3 in whole blood, plasma or serum, was not possible prior to the presently claimed Invention and that, as disclosed in the Declaration of Kathleen Pirollo, Applicants have unexpectedly discovered that it is possible to

determine the amount of cleaved 17 kDa fragment of caspase 3 in whole blood, serum or plasma. Applicants argue that a person of ordinary skill in the art, at the time of filing of the present application, would not have been able to detect the amount of the 17 kDa fragment of caspase 3 from whole blood, plasma or serum, due to the presence of interfering components, such as porphyrins.

Applicants arguments have been fully considered but are not persuasive. First, as evidenced by Kohler et al caspase activity may be measured by measuring the amount of activated caspases (which includes the 17k Da fragment of caspase 3) by immunoblot or by the cleavage of synthetic substrates (as measured in Mascarenhas). Both methods may be used interchangeably. Mascarenhas was able to differentiate the amount of apoptosis with different drug regimens by measuring caspase 3 activity. Thus, Mascarenhas was not just measuring the presence of the active 17 kDa fragment of caspase 3. Furthermore, Estrov et al (1998, IDS) did detect the 17k Da fragment of caspase 3 in peripheral blood low density cells using an immunoblot technique. (Figs. 1). As demonstrated by Sumpter et al, Applicants used a well known technique for purifying proteins away from contaminants to be able to more accurately measure the amount of the 17kDa fragment of caspase 3 in serum.

A person of ordinary skill in the art would have had a reasonable expectation of success in purifying and then detecting the 17k Da fragment of caspase 3 in whole blood, serum or plasma using a Biogel P6 column because this column was commonly used in the art to purify proteins away from contaminants.

Claims 5-14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas, in view of Jang et al Hayami et al, and Sumpter et al, as evidenced by Köhler et al, and further in view of Xu et al (previously cited).

The claims are drawn to a method for evaluating the efficacy of a therapeutic agent in the body of a mammal comprising obtaining a first sample of whole blood. plasma or serum, wherein said first sample can contain a 17 kDa fragment of caspase 3, wherein said first sample has been obtained from said mammal before administration

of said therapeutic agent to said mammal; purifying the first sample using column chromatography; assaying the first sample to determine the amount of the cleaved 17 kDa fragment present; administering said therapeutic agent to said mammal; obtaining a second sample of whole blood, plasma or serum, from the mammal; purifying the second sample using column chromatograph; and assaying the second sample to determine the amount of said 17kDa fragment present; wherein the therapeutic agent comprises a comprises a DNA molecule which encodes a wild type p53 molecule, wherein said therapeutic agent is administered as a complex with a ligand-cationic liposome, , wherein said ligand comprises an anti-transferrin receptor single chain antibody fragment, wherein said antibody fragment is an scFv fragment, wherein said liposome comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan- olamine (DOPE), wherein said therapeutic agent further comprises a chemotherapeutic agent or a radiotherapeutic agent.

Mascarenhas, Jang et al, Hayami et al, Sumpter et al, and Köhler have been described supra.

Neither Mascarenhas ,Jang et al, Hayami et al, Sumpter et al, nor Köhler disclose a p53 gene therapy comprising administering a p53 expression plasmid cationic immunolipolex system directed by a single-chain antibody Fv fragment against the transferrin receptor, wherein the immunoliplex complex comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan-olamine (DOPE) further in combination with a chemotherapeutic agent.

Xu et al disclose a systemic p53 gene therapy comprising administering a p53 expression plasmid cationic immunolipolex system directed by a single-chain antibody Fv fragment against the transferrin receptor, wherein the immunoliplex complex comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan- olamine (DOPE) further in combination with docetaxel (Abstract, page 724 1st and 2nd columns).

One of ordinary skill in the art would have been motivated to apply Xu et al's systemic p53 gene therapy to Mascarenhas, Jang et al, Hayami et al, Sumpter et al,

and Köhler's treatment and detection of apoptosis by caspase 3 activity because Xu et al disclose that sensitization of breast tumors to chemotherapeutic agents is due to the restoration of the apoptotic pathway (page 732, 2nd column). It would have been *prima facie* obvious to combine Mascarenhas, Jang et al, Hayami et al, Sumpter et al, and Köhler's treatment and detection of apoptosis by caspase 3 activity with Xu et al's systemic p53 gene therapy to measure apoptosis following the p53 gene therapy treatment.

Summary

Claims stand rejected

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 4/18/2007 and amendments to the claims prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from

8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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